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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,853	02/04/2004	Larry A. Sklar	N12-035US	3509

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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/771,853	SKLAR ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-55* is/are pending in the application.

4a) Of the above claim(s) *27-41 and 48-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/8/04, 11/17/04* 5/16/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments And/Or Claims:

Applicant's election with traverse of Group IV, consisting of claims 42, drawn to methods for evaluating GPCR agonism, antagonism or inactivity in a flow cytometric process in the reply filed on 8 May 2006 in response to Requirement for Restriction of 3 April 2006 is acknowledged. The traversal is on the ground(s) that all the originally filed claims, though patentably distinct, are related methods having a broad common utility and searching all the claimed inventions would not place a serious search burden on the Examiner. This is not found persuasive because although the Applicants' inventions (II-V) are all directed to binding assays to detect agonists or antagonists, they are drawn to four patentably distinct processes with different goals, different intermediate steps, and different end results, as set forth in the restriction requirement of 3 April 2006. The search of all these methods would not be co-extensive and each invention would require a unique search of the art. Applicant notes that the Patent Office did not present different classification schemes of the claimed Inventions. However, the Examiner's search will include not only the United States patent literature, but the foreign patent literature and non-patent literature as well. The search of the patent and non-patent literature will not be restricted by classification.

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 42-47 are under examination. Claims 27-41 and 48-55 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42, the independent claim of the instant invention, is drawn to a method of evaluating the relative G-protein agonism, antagonism or inactivity of a compound for G-protein coupled receptor (GPCR) in a single sample. Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps (See MPEP § 2172.01).

Claim 42 recites the steps of providing a sample suspension containing a detectable GPCR, a set of G protein beads and a set of ligand beads which will bind to GPCR, mixing the sample suspension with test compound, and detecting presence or absence of a complex between compound and GPCR. The claim recites that "a GPCR antagonist prevents binding of said detectable GPCR to said G-protein beads....and prevents binding of detectable GPCR to said ligand bead; a GPCR agonist allows binding of said detectable GPCR to said G-protein beads.....but prevents binding of said detectable GPCR to said ligand bead; and an inactive compound prevents binding of said detectable GPCR to said G protein beads .....but allows binding of said GPCR to said ligand bead." The claim recites a system comprising only one detectable moiety, a detectable GPCR. It is unclear how one would determine if the detectable GPCR is binding to G-protein beads or ligand beads in a system comprising both a set of G-protein beads and a set of ligand beads. Thus, carrying out the method steps would not result in accomplishing the goal set forth in the preamble, so it is unclear what the claim

is directed to. Additionally, Claim 42 recites "epitope-recognizing beads". It is unclear what applicant intends by "epitope-recognizing"; it is unclear whether applicant envisions an antibody-antigen interaction between antibody-coated beads and G-protein or some other type of reaction between the bead and the protein.

Furthermore, claim 42 recites a "detectable GPCR"; Claim 44 recites "a method of claim 42, wherein the fluorescent moiety is any fluorescent moiety fused to said G-protein coupled receptor". It is unclear whether the fluorescent moiety constitutes "detectable" label recited in claim 42 or an additional labeled component of the assay system.

Claim 45 recites wherein "a method of claim 43, wherein the detectable β2-adrenergic receptor is β2AR-GFP fusion protein". Claim 43 recites "wherein the G protein coupled receptor is a .....receptor containing a fluorescent moiety." It is unclear if the detectable receptor recited in Claim 45 constitutes the receptor containing a fluorescent moiety or an additional labeled component of the assay system.

Claim 47 contains the trademark/trade name Texas Red. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a fluorescent moiety and, accordingly, the identification/description is indefinite.

Claims 43 and 46 are included in this rejection as being dependent from a rejected claim.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim(s) 42-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Claim 42, the independent claim of the instant invention is drawn to a method of evaluating the relative G-protein receptor agonism, antagonism or inactivity of a compound for a G-protein coupled receptor (GPCR) in a single sample by flow cytometric process. The method comprises:

a. providing a sample suspension containing a detectable GPCR, a set of G-protein beads and a set of ligand beads which will bind to said detectable GPCR

b. mixing said suspension complex with said (test) compound

c. detecting the formation or absence of formation between said compound and said detectable GPCR

The claim recites that one can determine whether the test compound is an agonist, antagonist or inactive by the following criteria:

1. A GPCR antagonist prevents binding of detectable GPCR to G-protein beads and prevents binding of detectable GPCR to ligand bead

2. A GPCR agonist allows binding of detectable GPCR to G-protein beads but prevents binding of detectable GPCR to ligand bead

3. An inactive compound prevents binding of detectable GPCR to G protein beads but allows binding of detectable GPCR to ligand bead.

Neither the specification nor the working examples teach how to perform this method utilizing a system where only one detectable label is present. One of ordinary skill in the art would not be able to distinguish fluorescence caused by binding of the detectable GPCR to G-protein from fluorescence caused by binding of the detectable GPCR to ligand bead, and thus would be unable to distinguish between an agonist and an inactive compound.

The specification (page 8, lines 19-26 and Figure 7) discloses that simultaneous determination of agonist, antagonist, and inactive compounds requires duplex flow cytometry utilizing a system comprising a system of G-protein beads colored with Texas Red (a fluorescent moiety), DHA beads (ligand bead), β2AR-GFP fusion protein (detectable GPCR) and the test compound. The results section (page 67, last paragraph bridging page 68, 1st paragraph) teaches a method of simultaneous determination of agonist and antagonist that could be carried out in a single mixture of both beads (ligand and G-protein) in one well, sharing the same receptor and ligand (test compound) which would determine whether the test compound was an agonist, antagonist or inactive. The specification teaches "a sample of Ni beads was reacted with activated Texas Red, then coated with G proteins" (page 67, last paragraph). The disclosure then states "the inactive compound allows β2AR-GFP binding to DNA beads, but not ARG (agonist-receptor-G-protein ternary complex) formation; the agonist

prevents β2AR-GFP to DHA beads and allows ARG formation; and an antagonist blocks β2AR-GFP binding to DHA beads and does not promote ARG formation" (page 68, 1st paragraph). Thus the teachings of the specification and results teach that, in order to accomplish the goal stated in the method claims of the instant invention, the sample suspension requires the presence of both a **detectable GPCR** and **G-protein beads that are modified with a fluorescent moiety.** Thus, the skilled artisan would have to undertake undue experimentation to practice this invention as recited "providing a sample suspension containing a detectable GPCR, a set of G protein beads .....and a set of ligand beads".

Therefore, due to the large quantity of experimentation required to practice the instant invention in the absence of labeled G-beads and detectable GPCR, the lack of direction and guidance provided in the specification directed to the same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Prior art made of record:

The following prior art is made of record and not relied upon is considered pertinent to applicant's disclosure. Sarvazyan et al (2002, Biochemistry 41:12858-12867) teaches of method of using flow cytometry to measure the binding of fluorescently labeled Gα subunit binding to Gβγ in the presence of receptor-expressing cell membranes. Sklar, et al. (2000, Biotechniques 28:976-85) disclose a method of investigating G protein-coupled receptor-ligand interaction by detecting said interactions by flow cytometry. Sklar et al (2002. Annu Rev Biophyst Biomol Struct 31:97-119) generally discuss the use of high throughput flow cytometry to study ligand-receptor interactions and molecular assemblies. They teach that one of the interacting components be physically associated in a covalent or high-affinity state with beads to be analyzed, while the other component be visible to the cytometer (page 107, 2nd

paragraph). The reference teaches that a short hexahistidine tag added to the protein can be used to immobilize a protein directly onto an appropriate microsphere (page 108, 1st paragraph). The reference teactes fluorescent chimeric proteins can be created through molecular biology by fusing the protein of interest and GFP (page 109, 2nd paragraph). Additionally, the reference teaches the detection of many assemblies in a single sample using individual micospheres of different dyes (page 111, last paragraph bridging page 112, 1st paragraph).

However, none of the references, singularly or in combination, teach a method comprising evaluating the relative G-protein receptor agonism, antagonism or inactivity of a compound in a single sample by a flow cytometric process comprising providing a sample suspension containing a detectable GPCR, a set of G-protein beads and a set of ligand beads which will bind to said detectable GPCR, mixing said suspension complex with said (test) compound and detecting the formation or absence of formation between said compound and said detectable GPCR wherein a GPCR antagonist prevents binding of said detectable GPCR to said G-protein beads....and prevents binding of detectable GPCR to said ligand bead; a GPCR agonist allows binding of said detectable GPCR to said G-protein beads.....but prevents binding of said detectable GPCR to said ligand bead; and an inactive compound prevents binding of said detectable GPCR to said G protein beads .....but allows binding of said GPCR to said ligand bead.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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